

MEANS AND METHOD FOR A QUADRUPOLE SURFACE INDUCED  
DISSOCIATION QUADRUPOLE TIME-OF-FLIGHT MASS SPECTROMETER

1 TECHNICAL FIELD OF THE INVENTION

2       The present invention relates generally to means and method  
3 whereby ions from an ion source are selectively transmitted  
4 through a multipole apparatus having the capability of producing  
5 ion fragments via collisions with a surface or a gas to be  
6 readily analyzed by a TOF mass spectrometer. More specifically,  
7 a method and apparatus are described which use a plurality  
8 (preferably three) of multipole devices, a collision surface  
9 (for SID), and/or a collision gas (for CID) to produce fragment  
10 ions of a selected m/z range for subsequent mass analysis.

11  
12 BACKGROUND OF THE PRESENT INVENTION

13       The present invention relates to a multipole ion system with  
14 a collision surface for use in TOF mass spectrometry. The  
15 methods for transmitting ions and producing ion fragments  
16 described herein are enhancements of the techniques that are  
17 referred to in the literature relating to mass spectrometry.

18       Mass spectrometry is an important tool in the analysis of a  
19 wide range of chemical compounds. Specifically, mass

1 spectrometers can be used to determine the molecular weight of  
2 sample compounds. The analysis of samples by mass spectrometry  
3 consists of three main steps - formation of gas phase ions from  
4 sample material, mass analysis of the ions to separate the ions  
5 from one another according to ion mass, and detection of the  
6 ions. A variety of means exist in the field of mass spectrometry  
7 to perform each of these three functions. The particular  
8 combination of means used in a given spectrometer determine the  
9 characteristics of that spectrometer.

10 To mass analyze ions, for example, one might use a magnetic  
11 (B) or electrostatic (E) analyzer. Ions passing through a  
12 magnetic or electrostatic field will follow a curved path. In a  
13 magnetic field the curvature of the path will be indicative of  
14 the momentum-to-charge ratio of the ion. In an electrostatic  
15 field, the curvature of the path will be indicative of the  
16 energy-to-charge ratio of the ion. If magnetic and electrostatic  
17 analyzers are used consecutively, then both the momentum-to-  
18 charge and energy-to-charge ratios of the ions will be known and  
19 the mass of the ion will thereby be determined. Other mass  
20 analyzers are the quadrupole (Q), the ion cyclotron resonance  
21 (ICR), the time-of-flight (TOF), and the quadrupole ion trap

1 analyzers.

2 Before mass analysis can begin, however, gas phase ions must  
3 be formed from sample material. If the sample material is  
4 sufficiently volatile, ions may be formed by electron impact (EI)  
5 or chemical ionization (CI) of the gas phase sample molecules.  
6 For solid samples (e.g. semiconductors, or crystallized  
7 materials), ions can be formed by desorption and ionization of  
8 sample molecules by bombardment with high energy particles.  
9 Secondary ion mass spectrometry (SIMS), for example, uses keV  
10 ions to desorb and ionize sample material. In the SIMS process a  
11 large amount of energy is deposited in the analyte molecules. As  
12 a result, fragile molecules will be fragmented. This  
13 fragmentation is undesirable in that information regarding the  
14 original composition of the sample -- e.g., the molecular weight  
15 of sample molecules -- will be lost.

16 For more labile, fragile molecules, other ionization methods  
17 now exist. The plasma desorption (PD) technique was introduced  
18 by Macfarlane et al. in 1974 (Macfarlane, R. D.; Skowronski, R.  
19 P.; Torgerson, D. F., *Biochem. Biophys. Res Commoun.* **60** (1974)  
20 616). Macfarlane et al. discovered that the impact of high  
21 energy (MeV) ions on a surface, like SIMS would cause desorption

1 and ionization of small analyte molecules, however, unlike SIMS,  
2 the PD process results also in the desorption of larger, more  
3 labile species -- e.g., insulin and other protein molecules.

4 Lasers have been used in a similar manner to induce  
5 desorption of biological or other labile molecules. See, for  
6 example, VanBreeman, R.B.: Snow, M.: Cotter, R.J., *Int. J. Mass*  
7 *Spectrom. Ion Phys.* **49** (1983) 35; Tabet, J.C.; Cotter, R.J.,  
8 *Anal. Chem.* **56** (1984) 1662; or Olthoff, J.K.; Lys, I.: Demirev,  
9 P.: Cotter, R. J., *Anal. Instrument.* **16** (1987) 93. Cotter et  
10 al. modified a CVC 2000 time-of-flight mass spectrometer for  
11 infrared laser desorption of involatile biomolecules, using a  
12 Tachisto (Needham, Mass.) model 215G pulsed carbon dioxide laser.  
13 The plasma or laser desorption and ionization of labile molecules  
14 relies on the deposition of little or no energy in the analyte  
15 molecules of interest. The use of lasers to desorb and ionize  
16 labile molecules intact was enhanced by the introduction of  
17 matrix assisted laser desorption ionization (MALDI) (Tanaka, K.;  
18 Waki, H.; Ido, Y.; Akita, S.; Yoshida, Y.; Yoshica, T., *Rapid*  
19 *Commun. Mass Spectrom.* **2** (1988) 151 and Karas, M.; Hillenkamp,  
20 F., *Anal. Chem.* **60** (1988) 2299). In the MALDI process, an analyte  
21 is dissolved in a solid, organic matrix. Laser light of a

1 wavelength that is absorbed by the solid matrix but not by the  
2 analyte is used to excite the sample. Thus, the matrix is  
3 excited directly by the laser, and the excited matrix sublimates  
4 into the gas phase carrying with it the analyte molecules. The  
5 analyte molecules are then ionized by proton, electron, or cation  
6 transfer from the matrix molecules to the analyte molecules.  
7 This process, MALDI, is typically used in conjunction with time-  
8 of-flight mass spectrometry (TOFMS) and can be used to measure  
9 the molecular weights of proteins in excess of 100,000 daltons.

10 Time-of-flight mass spectrometry (or TOFMS) plays an  
11 important role in the analysis of chemical compounds.  
12 Specifically, TOF mass spectrometers are useful in determining  
13 the molecular weight of sample compounds. In orthogonal TOF mass  
14 spectrometers ions pass from the source into the analyzer in a  
15 direction which is orthogonal to the axis of the analyzer. The  
16 concept of orthogonal acceleration using TOFMS was disclosed by  
17 O'Hallran et al. in 1964 (G.J. O'Halloran et al., *Determination*  
18 *of Chemical Species Prevalent in a Plasma Jet*. Technical  
19 Documentary Report No. ASD-TDR-62-664, prepared under contract AF  
20 33(616)-8374 by the Bendix Corp. Research Laboratories (1964)).  
21 O'Hallran et al. also introduced the application of TOF mass

1 analysis to ionization sources at elevated pressure. One  
2 advantage to using orthogonal acceleration and elevated pressure  
3 ionization sources is that ions form a continuous beam and can be  
4 mass analyzed more efficiently. Also, with the "orthogonal  
5 acceleration" method, the mass analysis occurs along an axis  
6 which is orthogonal to the ion's initial direction of motion. As  
7 a result, the initial energy of the ions does not significantly  
8 degrade the mass resolution of the instrument.

9 Chien and Lubman demonstrated the advantage of using a  
10 quadrupole ion trap - TOF mass analyzer in the analysis of  
11 electrospray produced ions (Chien, B.M.; Lubman, D.M., *Anal.*  
12 *Chem.* **66**, 1630(1994)). The ions from the electrospray source are  
13 transferred with a high efficiency to the TOF analyzer and ions  
14 may be preselected and collision induced dissociation on these  
15 ions may be performed. One disadvantage with this method is low  
16 mass resolving power. Also, there are restrictions in the time  
17 required for cooling the ions and cycling the pressure in the ion  
18 trap.

19 Chernushevich et al discloses the use of ion introduction  
20 into an RF-quadrupole ion guide at a high gas pressure (I.V.  
21 Chernushevich, Proceedings of the 44th ASMS Conference of Mass

1 Spectrometry and Allied Topics, May 12-16, 1173 (1996)).  
2 Similarly, Douglas discloses ion introduction into a quadrupole  
3 ion trap rather than a TOF analyzer (D.J. Douglas, USPN  
4 5,179,278). Here, the ions are cooled by passage through the  
5 quadrupole at elevated pressure and are then transferred into a  
6 low pressure region containing a quadrupole trap analyzer. This  
7 "collisional focusing" method has also been incorporated with the  
8 "orthogonal acceleration" method in TOF mass spectrometry to  
9 obtain a higher resolution mass spectrum.

10 Morris et al. discloses the use of additional multipole  
11 devices to preselect ions and induce collision dissociation in  
12 the trap - TOF analyzer (H.R. Morris et al., *Rapid Comm. Mass*  
13 *Spectrom.* 10, 889(1996)). Their first multipole device is used  
14 to cool ions then a second multipole is used for mass selection,  
15 and a third multipole is used for collision induced dissociation.  
16 Collision induced dissociation experiments were also disclosed in  
17 Lubman (B.M. Chien, S.M. Michael, D.M. Lubman, *Int J. Mass*  
18 *Spectrom. Ion Process.*, 131, 149 (1994), B.M. Chien, D.M. Lubman,  
19 *Anal. Chem.* 66, 1630 (1994)).

20 Ions extracted from a multipole device and orthogonally  
21 accelerated in the direction of the axis of the analyzer will

1 have a significant kinetic energy orthogonal to the axis of the  
2 analyzer. This initial kinetic energy will cause the ions to  
3 drift perpendicularly to the analyzer axis. This kinetic energy  
4 must be accounted for in order to prevent ion loss and to ensure  
5 ion detection. M.A. Park discloses a multideflector for  
6 correcting for such kinetic energies by deflecting the ion beam  
7 on the analyzer axis (US patents 5,696,375 and 6,107,625).

8 Also, during the extracting process, the kinetic energy  
9 component of ions in the direction along the axis of the TOF  
10 analyzer - and therefore orthogonal to the axis of the multipole  
11 ion guide - will have a strong influence on the resolution that  
12 can be achieved by a TOF analyzer. To achieve best results, ions  
13 should be have near thermal kinetic energies - achieved by  
14 cooling in the ion guide.

15 High efficiency in transmitting ions from a multipole to a  
16 TOF analyzer requires that the spatial extent of the ion beam  
17 perpendicular to the axis of the analyzer be large compared to,  
18 for example, that of prior art MALDI-TOF designs. As a result,  
19 some prior art devices (i.e. the two stage reflectron taught by  
20 R. Frye in USPN 4,731,532) cannot be used with the orthogonal  
21 multipole orthogonal TOF instruments described above.



1       An alternative "method and device for orthogonal ion  
2 injection into a time-of-flight mass spectrometer", proposed in  
3 Franzen United States Pat. No. 5,763,878 (the "'878 patent").  
4 According to the '878 patent, ions are ejected from a multipole  
5 ion guide of design similar to that of Chernushevich et al. into  
6 a time-of-flight analyzer and in a direction orthogonal to the  
7 axis of the multipole device. In trapping mode an RF potential  
8 is applied to the poles of the multipole device whereas in  
9 ejection mode, DC potentials are applied to the poles of the  
10 multipole device so as to accelerate the ions in a direction  
11 orthogonal to the axis of the multipole device and parallel to  
12 the axis of the TOF analyzer.

13       Atmospheric pressure ionization (API) includes a number of  
14 methods. Typically, analyte ions are produced from liquid  
15 solution at atmospheric pressure. One of the more widely used  
16 methods, known as electrospray ionization (ESI), was first  
17 suggested by Dole et al. (M. Dole, L.L. Mack, R.L. Hines, R.C.  
18 Mobley, L.D. Ferguson, M.B. Alice, *J. Chem. Phys.* **49**, 2240,  
19 1968). In the electrospray technique, analyte is dissolved in a  
20 liquid solution and sprayed from a needle. The spray is induced  
21 by the application of a potential difference between the needle

1 and a counter electrode. The spray results in the formation of  
2 fine, charged droplets of solution containing analyte molecules.  
3 In the gas phase, the solvent evaporates leaving behind charged,  
4 gas phase, analyte ions. Very large ions can be formed in this  
5 way. Ions as large as 1 MDa have been detected by ESI in  
6 conjunction with mass spectrometry (ESMS).

7 ESMS was introduced by Yamashita and Fenn (M. Yamashita and  
8 J.B. Fenn, *J. Phys. Chem.* **88**, 4671, 1984). To establish this  
9 combination of ESI and MS, ions had to be formed at atmospheric  
10 pressure, and then introduced into the vacuum system of a mass  
11 analyzer via a differentially pumped interface. The combination  
12 of ESI and MS afforded scientists the opportunity to mass analyze  
13 a wide range of samples. ESMS is now widely used primarily in  
14 the analysis of biomolecules (e.g. proteins) and complex organic  
15 molecules.

16 In the intervening years a number of means and methods  
17 useful to ESMS and API-MS have been developed. Specifically,  
18 much work has focused on sprayers and ionization chambers. In  
19 addition to the original electrospray technique, pneumatic  
20 assisted electrospray, dual electrospray, and nano electrospray  
21 are now also widely available. Pneumatic assisted electrospray

1 (A.P. Bruins, T.R. Covey, and J.D. Henion, Anal. Chem. 59, 2642,  
2 1987) uses nebulizing gas flowing past the tip of the spray  
3 needle to assist in the formation of droplets. The nebulization  
4 gas assists in the formation of the spray and thereby makes the  
5 operation of the ESI easier. Nano electrospray (M.S. Wilm, M.  
6 Mann, *Int. J. Mass Spectrom. Ion Processes* 136, 167, 1994)  
7 employs a much smaller diameter needle than the original  
8 electrospray. As a result the flow rate of sample to the tip is  
9 lower and the droplets in the spray are finer. However, the ion  
10 signal provided by nano electrospray in conjunction with MS is  
11 essentially the same as with the original electrospray. Nano  
12 electrospray is therefore much more sensitive with respect to the  
13 amount of material necessary to perform a given analysis.

14 An elevated pressure ion source always has an ion production  
15 region (wherein ions are produced) and an ion transfer region  
16 (wherein ions are transferred through differential pumping stages  
17 and into the mass analyzer). The ion production region is at an  
18 elevated pressure -- most often atmospheric pressure -- with  
19 respect to the analyzer. The ion production region will often  
20 include an ionization "chamber". In an ESI source, for example,  
21 liquid samples are "sprayed" into the "chamber" to form ions.

1        Once the ions are produced, they must be transported to the  
2 vacuum for mass analysis. Generally, mass spectrometers (MS)  
3 operate in a vacuum between  $10^{-4}$  and  $10^{-10}$  torr depending on the  
4 type of mass analyzer used. In order for the gas phase ions to  
5 enter the mass analyzer, they must be separated from the  
6 background gas carrying the ions and transported through the  
7 single or multiple vacuum stages.

8        The use of multipole ion guides has been shown to be an  
9 effective means of transporting ions through a vacuum system.  
10 Publications by Olivers et al. (Anal. Chem, Vol. 59, p. 1230-  
11 1232, 1987), Smith et al. (Anal. Chem. Vol. 60, p. 436-441, 1988)  
12 and Douglas et al. U.S. Pat. No. 4,963,736 (Douglas) have  
13 reported the use of AC-only quadrupole ion guides to transport  
14 ions from an API source to a mass analyzer. Such multipole ion  
15 guides may be configured as collision cells capable of being  
16 operated in RF only mode with a variable DC offset potential  
17 applied to all rods. Thomson et al., U.S. Patent Number  
18 5,847,386 (Thomson) also describes a quadrupole ion guide. The  
19 ion guide of Thomson is configured to create a DC axial field  
20 along its axis to move ions axially through a collision cell,  
21 *inter alia*, or to promote dissociation of ions (i.e., by

1 Collision Induced Dissociation (CID)).

2 Further, mass spectrometers similar to that of Whitehouse et  
3 al. U.S. Patent No. 5,652,427, entitled "Multipole Ion Guide for  
4 Mass Spectrometry", (Whitehouse) use multipole RF ion guides to  
5 transfer ions from one pressure region to another in a  
6 differentially pumped system. In the source of Whitehouse, ions  
7 are produced by ESI or APCI at substantially atmospheric  
8 pressure. These ions are transferred from atmospheric pressure  
9 to a first differential pumping region by the gas flow through a  
10 glass capillary. Ions are transferred from this first pumping  
11 region to a second pumping region through a "skimmer" by an  
12 electric field between these regions as well as gas flow. A  
13 multipole in the second differentially pumped region accepts ions  
14 of a selected mass/charge ( $m/z$ ) ratio and guides them through a  
15 restriction and into a third differentially pumped region. This  
16 is accomplished by applying AC and DC voltages to the individual  
17 poles.

18 A four vacuum stage ES/MS quadrupole mass spectrometer  
19 according to Whitehouse, incorporating a multipole ion guide  
20 beginning in one vacuum pumping stage and extending contiguously  
21 into an adjacent pumping stage, is depicted in FIG. 1. As

1 discussed above, ions are formed from sample solution by an  
2 electrospray process when a potential is applied between spray  
3 needle 5 of sprayer 2 and sampling orifice 4. In other words,  
4 sample solution enters the ionization chamber through spray  
5 needle 5, at the end of which the solution is formed into a spray  
6 of fine droplets (not shown). The spray is formed as a result of  
7 an electrostatic field applied between spray needle 5 and  
8 sampling orifice 7. The sampling orifice may be an aperture,  
9 capillary, or other similar inlet leading into the differential  
10 pumping regions of the mass spectrometer. According to the prior  
11 art system shown in FIG. 1, capillary 16 is used to transport  
12 ions from atmospheric pressure region 1, where the ions are  
13 formed, to first pumping region 6. Lenses 10 and 14 are used to  
14 guide the ions from the exit end of capillary 16 through third  
15 pumping region 22 into a fourth pumping region 26 containing a  
16 mass analyzer -- in this case a quadrupole mass analyzer.

17 Between lenses 10 and 30, an RF only hexapole ion guide 20  
18 is used to guide ions through differential pumping stages 22 and  
19 26 to exit 28 and into mass analysis region 32 through orifice  
20 34. Ion guide 20 according to this prior art design is intended  
21 to provide for the efficient transport of ions from one location

1 (i.e., the entrance of skimmer 14) to a second location (i.e.,  
2 orifice 34). For the purpose of illustration, an electrospray  
3 ion source is shown as the API source. This could alternatively  
4 be an APCI or an ICP source.

5 Sample liquid is introduced through the electrospray needle  
6 2 and is electrosprayed - either with or without pneumatic  
7 assistance - into chamber 1 as it exits needle 2. The charged  
8 droplets produced evaporate and desorb gas phase ions both in  
9 chamber 1 and as they are swept into vacuum through the annulus  
10 in capillary 16. A portion of the ions that enter first vacuum  
11 stage 6 through the capillary exit are focused through skimmer 14  
12 with the help of lens 10 and the potential set on the capillary  
13 exit. Ions passing through skimmer 14 enter the multipole ion  
14 guide 20 which begins in vacuum pumping stage 22 and extends  
15 unbroken into vacuum stage 26. Ions falling within a certain m/z  
16 range - determined in part by the frequency and amplitude of the  
17 potentials applied to ion guide 20 - which enter multipole ion  
18 guide 20 will be guided to multipole ion guide exit end 28 and  
19 will be focused by exit lens 30 into the TOF analyzer region 32  
20 through orifice 34 for subsequent analysis. Whitehouse also  
21 discloses the use of collisional gas within ion guide 20 to cool

1 the ions to thermal velocities through collisional cooling.

2 In the scheme of Whitehouse, an RF only potential is applied  
3 to ion guide 20. As a result, ion guide 20 is not "selective"  
4 but rather transmits ions over a broad range of mass-to-charge  
5 (m/z) ratios. Such a range as provided by prior art multipoles  
6 is inadequate for certain applications, such as for Matrix  
7 Assisted Laser Desorption/Ionization (MALDI), because the ions  
8 produced may be well out of this m/z range. In other words, high  
9 m/z ions such as are often produced by the MALDI ionization  
10 method are often out of the range of transmission of conventional  
11 multipole ion guides.

12 Thus, electric voltages usually applied to the conventional  
13 ion guide are used to transmit ions from an entrance end to an  
14 exit end. Analyte ions produced in the ion production region  
15 pass through a capillary or other ion transfer device to move the  
16 ions to a differentially pumped region and enter the ion guide at  
17 the entrance end. Through collisions with gas in the ion guide,  
18 the kinetic energy of the ions is reduced to thermal energies.  
19 Simultaneously, the RF potential on the poles of the ion guide  
20 forces ions to the axis of the ion guide. Then, ions migrate  
21 through the ion guide toward its exit end, where the ions



1 typically either enter a second ion guide or enter the mass  
2 analysis region.

3 Whitehouse also discloses use of two or more ion guides in  
4 consecutive vacuum pumping stages to allow different DC and RF  
5 values. However, losses in ion transmission efficiency may occur  
6 in the region of static voltage lenses between ion guides. For  
7 example, a commercially available API/MS instrument manufactured  
8 by Hewlett Packard incorporates two skimmers and an ion guide.  
9 The region between the skimmers is pumped by the drag stage of  
10 the same turbopump which pumps the region containing the  
11 multipole ion guide. That is, an additional pumping stage/region  
12 is added without the addition of an extra turbo pump, and  
13 therefore, improved pumping efficiency may be achieved. In this  
14 dual skimmer design, there is no ion focusing device between  
15 skimmers, therefore ion losses may occur as the gases are pumped  
16 away. A second example is demonstrated by a commercially  
17 available API/MS instrument manufactured by Finnigan which  
18 applies an electrical static lens between capillary and skimmer  
19 to focus the ion beam. Due to narrow mass range of the static  
20 lens, the instrument may need to scan the voltage to optimize the  
21 ion transmission.

1 In addition, the electrode rods of the prior art multipole  
2 ion guides described above are positioned in parallel and are  
3 equally spaced at a common radius from the centerline of the ion  
4 guide. Thus, ions with a  $m/z$  ratio that fell within the ion  
5 guide stability window established by the applied voltages would  
6 have stable trajectories within the ion guide's internal volume  
7 bounded by the parallel, evenly spaced rods. This is true for  
8 quadrupoles, hexapoles, etc.

9 In other schemes a multipole might be used to guide ions of  
10 a selected  $m/z$  through the transfer region. For example, Morris  
11 et al., in H.R. Morris et al., High Sensitivity Collisionally  
12 Activated Decomposition Tandem Mass Spectrometry on a Novel  
13 Quadrupole/Orthogonal-Acceleration Time-of-Flight Mass  
14 Spectrometer, *Rapid Commun. Mass Spectrom.* **10**, 889 (1996), use a  
15 series of multipoles in their design. One of these is a  
16 quadrupole. The quadrupole can be run in a "wide bandpass" mode  
17 or a "narrow bandpass" mode. In the wide bandpass mode, an RF-  
18 only potential is applied to the quadrupole and ions of a  
19 relatively broad range of  $m/z$  values are transmitted. In narrow  
20 bandpass mode both RF and DC potentials are applied to the  
21 quadrupole such that ions of only a narrow range of  $m/z$  values are

1 selected for transmission through the quadrupole. In subsequent  
2 multipoles, the selected ions may be activated towards  
3 dissociation. In this way the instrument of Morris et al. is  
4 able to perform MS/MS experiments with a first mass analysis and  
5 subsequent fragmentation occurring in what would otherwise be  
6 simply a set of multipole ion guides.

7 Such a prior art ionization source according to Morris et  
8 al. is shown in FIG. 2. This prior art source design is similar  
9 to Whitehouse (as shown in FIG. 1), except for the multipole ion  
10 guide arrangement. In the prior art source design according to  
11 Morris et al., four RF multipoles 48, 50, 52 & 54 are used. The  
12 first multipole encountered by the ions is hexapole 48. It is  
13 used in a manner similar to the Whitehouse et al. to cool and  
14 guide the ions. The second multipole encountered is quadrupole  
15 50. Quadrupole 50 can be used in a wide bandpass mode to  
16 transmit ions over a broad m/z range, or in a narrow bandpass  
17 mode to transmit ions of a selected narrow m/z range. This leads  
18 to the use of the mass spectrometer instrument in MS and MS/MS  
19 modes. In MS mode, quadrupole 50 is operated as a wide bandpass  
20 ion guide. Ions are simply transmitted by all four multipoles  
21 48, 50, 52 & 54 to time-of-flight mass analyzer 62. The TOF mass

1 analyzer 62 is then used to produce a mass spectrum. In MS/MS  
2 mode, quadrupole 50 is operated as a narrow bandpass ion guide to  
3 select ions of interest.

4 Further, the ions encounter a third multipole -- hexapole 52  
5 -- which is operated with a DC offset with respect to quadrupole  
6 50 and contains a collision gas. This leads to collisions  
7 between the ions of interest and the collision gas and can result  
8 in the formation of fragment ions. Finally, the fragment ions  
9 are guided by a fourth multipole -- hexapole 54 -- to TOF  
10 analyzer 62 which is then used to produce a mass spectrum of  
11 these fragment ions.

12 In the performance of tandem mass spectrometry experiments,  
13 precursor ions are selected and fragmented, and the fragment ions  
14 are analyzed to produce a fragment ion spectrum. In the prior  
15 art, a variety of methods have been used to fragment precursor  
16 ions. Among these are collision induced dissociation (CID) as  
17 mentioned above, surface induced dissociation (SID), infrared  
18 multiphoton dissociation (IRMPD), electron capture dissociation  
19 (ECD), and many others. Each of these methods has its advantages  
20 and disadvantages. For example, CID is a relatively simple  
21 technique and can be applied in a variety of instrument

1 configurations (i.e. quadrupole, TOF, or FT-ICR analyzers). IRMPD  
2 is somewhat more complex in that a laser is required, but has the  
3 advantage that it produces no gas load on the vacuum system - as  
4 is the case in CID - and can produce fragment species that are  
5 inaccessible by CID. SID is also somewhat complex in that it is  
6 necessary that a "collision surface" be prepared and placed in  
7 the instrument. Also, SID is not readily adaptable to all types  
8 of analyzers. However, SID does provides better control over the  
9 fragmentation process and can lead to higher efficiency in the  
10 production of useful fragment ions.

11       Quadrupole mass analyzers have been used in conjunction with  
12 surface induced dissociation (SID). For example, Wysocki et al.  
13 discloses such an arrangement (Chungang GU, Vincent J. Angelico,  
14 Vicki H. Wysocki, Proceedings of the 46<sup>th</sup> ASMS conference on Mass  
15 Spectrometry and Allied Topics, pg. 72(1998), Wysocki et al.,  
16 Proceedings of the 47<sup>th</sup> ASMS Conference on Mass Spectrometry and  
17 Allied Topics, pg. 2834, 2144, 1040, and 2299(1999), Ahok Dongre,  
18 Vicki Wysocki, *Org. Mass Spectrom.* **29**, 700(1994), Thomas Kane,  
19 Vincent Angelico, and Vicki Wysocki, *Langmuir* **13**, 6722(1997),  
20 Chungang Gu, Vicki Wysocki, *J. AM. Chem. Soc.* **119**, 12010(1997),  
21 Arpad Somogyi, Thomas Kane, Jian-Mei Ding, Vicki Wysocki, *J. AM.*

1 *Chem. Soc.* **115**, 5275(1993), Thomas Kane, Vincent Angelico, Vicki  
2 Wysocki, *Anal. Chem.* **66**, 3733(1994), Thomas Kane, Vicki Wysocki,  
3 *Int. J. Mass. Spectrom. Ion Process* **140**, 177(1994), Vicki Wysocki  
4 et al., *Am. Soc. Mass. Spectrom.* **3**, **27**(1992)). In such an  
5 arrangement, as shown in FIG. 3, first quadrupole 81 comprising  
6 rods 80 is used to select ions of a given m/z from a beam of  
7 incoming ions 78. The selected ions are allowed to collide with  
8 a SID "collision surface" 76 after passing through electrodes 82.  
9 The instrument according to Wysocki can be operated without  
10 fragmentation of the selected ions or with surface-induced  
11 dissociation of the selected ions. In SID, the ions are  
12 dissociated via energetic collisions with a prepared "collision  
13 surface". This collision results in the fragmentation of the  
14 selected ions into "fragment ions", and the fragment ions are  
15 extracted (and focused by electrodes 84) into second quadrupole  
16 85 comprising rods 86. Second quadrupole 85 is used to analyze  
17 the these fragment ions.

18 In MS mode, or to produce simply a mass spectrum of the  
19 incident ion beam, first quadrupole 81 is scanned over the mass  
20 range of interest while second quadrupole 85 is operated in broad  
21 bandpass mode (i.e., RF only). The potential between the source

1 (not shown) and collision surface 76 is held at zero volts. As a  
2 result, ions exiting first quadrupole 81 do not strike collision  
3 surface 76, but rather, these ions are deflected into second  
4 quadrupole 85 which transmits them to a detector (not shown).

5 In SID MS/MS mode, first quadrupole 81 is used to select  
6 ions of a given  $m/z$  out of the incident ion beam. These ions are  
7 allowed to strike collision surface 76. The kinetic energy of  
8 the ions when they strike surface 76 is determined largely by the  
9 potential difference between the ion source (not shown) and  
10 collision surface 76. Fragment ions resulting from the ion-  
11 surface collision are extracted by an electrostatic field into  
12 second quadrupole 85 where they are mass analyzed to produce a  
13 fragment ion spectrum.

14 For example, FIGs. 4A-D depict the operation of the Q-SID-Q  
15 instrument according to Wysocki without fragmentation due to SID  
16 (FIGs. 4A-B) and with fragmentation due to SID (FIGs. 4C-D). In  
17 MS mode, as shown in FIGs. 4A-B, no potential difference is  
18 applied between source 90 and collision surface 96. In this  
19 case, the ions are transmitted from source 90 through quadrupole  
20 92, but do not strike collision surface 96 (as indicated by ion  
21 path 94) and do not produce fragment ions. The ions then enter

1 quadrupole 98 for mass analysis. Therefore, because no fragment  
2 ions are produced, the resulting mass spectrum 120 shown in FIG.  
3 4B contains a single peak 100 -- that of the incident beam.

4 In SID MS/MS mode, as shown in FIGs. 4C-D, a potential  
5 difference is applied between source 102 and collision surface  
6 108. In this case, selected ions are transmitted from source 102  
7 through ion guide 104, such that they strike collision surface  
8 108 (at location 106 of the ion beam path). As a result of the  
9 collision, ion fragments of the initial ion beam are formed (as  
10 indicated at ion beam 110) and enter second quadrupole 112.  
11 Second quadrupole 112 is used to mass analyze the fragment ion.  
12 Once analyzed, these fragment ions then enter the detector (not  
13 shown). The resulting sharp peaks 114 of the mass spectrum 116  
14 shown in FIG. 4D depicts multiple  $m/z$  values of the fragment  
15 ions.

16 The present invention provides means and method of using SID  
17 in conjunction with any mass analyzer - in the preferred  
18 embodiment, a TOF mass analyzer. More specifically, a first  
19 multipole (preferably a quadrupole) is used to select precursor  
20 ions, the ions are allowed to collide with a collision surface,  
21 and the fragment ions thereby produced are collisionally cooled



1 in a second multipole and then mass analyzed in a mass analyzer  
2 (preferably a TOF mass analyzer). Further, a method and  
3 apparatus are described which use a plurality (preferably three)  
4 of multipole devices, a collision surface (for SID), and/or a  
5 collision gas (for CID) to produce fragment ions of a selected  
6 m/z range (i.e., using a Q-SID-Q or Q-CID-Q arrangement) for  
7 subsequent mass analysis (preferably in an orthogonal TOF mass  
8 analyzer).

#### 10 SUMMARY OF THE INVENTION

11 The purpose of the present invention is to provide a tandem  
12 mass spectrometry instrument with improved performance  
13 characteristics over prior art instruments. Particularly, the  
14 preferred embodiment Q-SID-Q-TOF instrument according to the  
15 present invention is capable of surface induced dissociation, and  
16 collision induced dissociation. Thus, an instrument according to  
17 the present invention can be used to take advantage of the  
18 fragmentation characteristics of either of these methods. Also,  
19 because a TOF mass analyzer is used in the preferred embodiment,  
20 precursor and fragment ion spectra can be obtained rapidly - i.e.

1 on a time scale consistent with hyphenation of the instrument  
2 with liquid chromatography.

3 Another object of the present invention is to provide a  
4 means of adapting surface induced dissociation to any type of  
5 mass analyzer. That is, SID is performed between two multipoles -  
6 e.g. Q-SID-Q - followed by mass analysis in a mass analyzer of  
7 choice - e.g. FT-ICR, quadrupole trap, etc.

8 Other objects, features, and characteristics of the present  
9 invention, as well as the methods of operation and functions of  
10 the related elements of the structure, and the combination of  
11 parts and economies of manufacture, will become more apparent  
12 upon consideration of the following detailed description with  
13 reference to the accompanying drawings, all of which form a part  
14 of this specification.

15  
16 BRIEF DESCRIPTION OF THE DRAWINGS

17 A further understanding of the present invention can be  
18 obtained by reference to a preferred embodiment set forth in the  
19 illustrations of the accompanying drawings. Although the  
20 illustrated embodiment is merely exemplary of systems for  
21 carrying out the present invention, both the organization and

1 method of operation of the invention, in general, together with  
2 further objectives and advantages thereof, may be more easily  
3 understood by reference to the drawings and the following  
4 description. The drawings are not intended to limit the scope of  
5 this invention, which is set forth with particularity in the  
6 claims as appended or as subsequently amended, but merely to  
7 clarify and exemplify the invention.

8 For a more complete understanding of the present invention,  
9 reference is now made to the following drawings in which:

10 FIG. 1 shows a conventional four vacuum stage ES/MS  
11 quadrupole MS instrument according to Whitehouse;

12 FIG. 2 shows a prior art ionization source design according  
13 to Morris;

14 FIG. 3 is a schematic representation of a prior art Q-SID-Q  
15 instrument according to Wysocki;

16 FIGs. 4A and 4B depict the operation of the Q-SID-Q  
17 instrument of FIG. 3 without fragmentation;

18 FIG. 4C and 4D depict the operation of the Q-SID-Q  
19 instrument of FIG. 3 with fragmentation (due to SID);

20 FIG. 5 is a diagrammatic representation of the preferred  
21 embodiment of the Q-SID-Q-TOF mass spectrometer according to the

1 present invention;

2 FIG. 6 is a diagrammatic representation of an alternate  
3 embodiment of the Q-SID-Q-TOF mass spectrometer according to the  
4 present invention.

5  
6 DETAILED DESCRIPTION OF A PREFERRED EMBODIMENT

7 As required, a detailed illustrative embodiment of the  
8 present invention is disclosed herein. However, techniques,  
9 systems and operating structures in accordance with the present  
10 invention may be embodied in a wide variety of forms and modes,  
11 some of which may be quite different from those in the disclosed  
12 embodiment. Consequently, the specific structural and functional  
13 details disclosed herein are merely representative, yet in that  
14 regard, they are deemed to afford the best embodiment for  
15 purposes of disclosure and to provide a basis for the claims  
16 herein which define the scope of the present invention. The  
17 following presents a detailed description of a preferred  
18 embodiment (as well as some alternative embodiments) of the  
19 present invention.

20 Referring first to FIG. 5, shown is diagrammatic  
21 representation of the preferred embodiment of the Q-SID-Q-TOFMS

1 according to the present invention. Specifically, the preferred  
2 embodiment of a quadrupole surface induced dissociation  
3 quadrupole time-of-flight ("Q-SID-Q-TOF") mass spectrometer  
4 according to the invention comprises ionization source 130, first  
5 multipole 132 (preferably a hexapole), second multipole  
6 (preferably a quadrupole) 140, collision surface 136 for surface  
7 induced dissociation (SID), third multipole 138 (which optionally  
8 acts as a collision cell for collision induced dissociation  
9 (CID)), and mass analyzer 142 (preferably a time of flight mass  
10 analyzer). Multipoles 132, 140, and 138 are preferably RF  
11 multipoles similar to the RF multipole ion guides known in the  
12 prior art.

13 As shown, first multipole 132 is disposed coaxial with and  
14 downstream of ion source 130. Second multipole 140 is disposed  
15 coaxial with and downstream of first multipole 132 and ion source  
16 130, such that ions 134 are transported from ion source 130  
17 through first multipole 132 into second multipole 140. Third  
18 multipole 138 preferably contains a collision gas and is  
19 positioned such that its axis is orthogonal to the axis of first  
20 and second multipoles 132 & 140. Collision surface 136 is  
21 disposed between second and third multipoles 140 & 138 with its

1 normal vector at an angle (preferably  $45^\circ$ ) to the axis of  
2 multipoles 140 & 138. Finally, TOF analyzer 142 is disposed  
3 downstream of (and preferably orthogonal to) third multipole 138.

4 In the preferred embodiment, ion source 130 is an  
5 electrospray ionization (ESI) source. Ions are produced at  
6 atmospheric pressure and introduced into the vacuum system of the  
7 instrument through an aperture or other opening in the vacuum  
8 housing. Multipoles 132, 140, and 138 and analyzer 142 are  
9 preferably disposed in different pumping regions of the vacuum  
10 system. Multipole 132 in a first pumping region is maintained at  
11 a pressure of  $10^{-2} - 10^{-3}$  mbar. Multipole 140 and collision  
12 surface 136, in a second pumping region, are maintained at a  
13 pressure of about  $10^{-5}$  mbar. Multipole 138, in a third pumping  
14 region, is maintained at a pressure of  $10^{-2} - 10^{-3}$  mbar. In the  
15 preferred embodiment, the pressure in multipole 138 is achieved  
16 by "leaking" a desired collision gas (e.g.  $N_2$ , Ar, He, etc.) into  
17 the multipole. A dynamic equilibrium between the rate at which  
18 gas is leaked into the multipole and the rate at which it is  
19 pumped away and a desired pressure is thereby achieved. Analyzer  
20 142 (preferably a TOF mass analyzer) is preferably maintained in  
21 a fourth pumping region at a pressure of  $10^{-7}$  mbar or less.

1 In the present invention, ions may be generated in any  
2 conceivable ion source (i.e., an electrospray ionization source,  
3 matrix assisted laser desorption/ionization, chemical ionization,  
4 etc.). As these ions enter first multipole 132, they undergo  
5 collisions with the gas therein. These collisions cause the ions  
6 to lose kinetic energy and thereby to be cooled to near thermal  
7 velocities. First multipole 132 guides the ions from the source  
8 region to the entrance of second multipole 140.

9 In second multipole 140, ions of a desired mass-to-charge  
10 ratio ( $m/z$ ) range are selected. Ions falling outside the desired  
11  $m/z$  range are removed from the ion beam by the electric field of  
12 multipole 140. Second multipole 140 is preferably a quadrupole.  
13 To transmit ions over a broad range of  $m/z$  values, the DC  
14 potential between the quadrupole rods is set to 0V and multipole  
15 140 is thereby operated in "RF only" mode. Multipole 140 is  
16 typically operated in RF only mode when generating a precursor  
17 ion spectrum. To select ions of a narrow  $m/z$  range, both RF and  
18 DC potentials are applied between the multipole rods as described  
19 extensively in the prior art. Multipole 140 is typically operated  
20 to select a narrow  $m/z$  range when generating a fragment ion  
21 spectrum.

1 In the performance of SID experiments, selected ions (aka.  
2 precursor ions) collide with collision surface 136 with a  
3 predefined collision energy. The collision surface may consist of  
4 a self assembled monolayer (preferably of straight chain  
5 hydrocarbons with fluorinated end groups). The preparation and  
6 use of collision surfaces for SID is described extensively in the  
7 literature. The predefined collision energy is given by the  
8 difference in the DC levels between multipole 132 and collision  
9 surface 136 (e.g. 20V). As detailed in prior art literature, a  
10 number of reactions can take place as a result of the ion-surface  
11 collision. Among these are neutralization, abstraction, and  
12 fragmentation. Products species (ideally fragment ions) are  
13 focused into multipole 138 by the potential difference between  
14 surface 136 and multipole 138 and by other ion optical elements  
15 (not shown) known in the prior art. Through collisions with gas  
16 in multipole 138, the fragment and remaining precursor ions are  
17 cooled to thermal energies. Multipole 138 guides the cooled ions  
18 to analyzer 142. Mass analyzer 142 (preferably a TOF analyzer) is  
19 then used to generate a mass spectrum of the ions - aka. a  
20 fragment ion spectrum.

21 Alternatively, in "MS only" analyses and in the performance



1 of CID experiments, the DC potential difference between multipole  
2 132 and collision surface 136 is maintained at 0V. Selected ions  
3 then do not collide with collision surface 136, but rather  
4 continue on into multipole 138. In "MS only" analyses, second  
5 multipole 140 is typically operated in RF only mode to transmit  
6 ions over a broad m/z range. The kinetic energy of ion entering  
7 multipole 138 is low - e.g. 5 eV. Through collisions with gas in  
8 multipole 138, the ions are again cooled to thermal energies.  
9 Multipole 138 guides the cooled ions to analyzer 142. Mass  
10 analyzer 142 (preferably a TOF analyzer) is used to generate a  
11 mass spectrum of the ions.

12 In the performance of CID experiments, the kinetic energy of  
13 ions entering multipole 138 is high - e.g. 100 eV. This kinetic  
14 energy is set by the DC potential difference between multipoles  
15 132 and 138. Through initial collisions with gas (e.g. N<sub>2</sub>, Ar,  
16 etc.) in multipole 138, ions are activated towards fragmentation.  
17 Fragment ions resulting from CID, as well as precursor ions, are  
18 then "cooled" to thermal energies via subsequent collisions with  
19 the gas in multipole 138. Multipole 138 also guides the ions  
20 into mass analyzer 142. Mass analyzer 142 (preferably a TOF  
21 analyzer) subsequently analyzes the fragment and precursor ions

1 and produces a fragment ion spectrum.

2 Furthermore, alternate embodiments of the present invention  
3 are not limited to three multipoles. Multipoles consisting of  
4 any number of rods may be used instead of quadrupoles. Also,  
5 ions selected by multipole 140 may be used as primary ions in the  
6 production of secondary ions from surface 136. In this way, the  
7 instrument may be used for SIMS analysis of a solid sample. That  
8 is, samples are deposited on a holder to form surface 136. Ions  
9 selected by multipole 140 collide with the sample inducing the  
10 sputtering of sample ions from sample material composing surface  
11 136. These ions are focused into multipole 138, cooled by  
12 collisions with the gas in multipole 138 and guided into analyzer  
13 142. Mass analyzer 142 (preferably a TOF analyzer) then produces  
14 a mass spectrum from these ions - i.e. a secondary ion mass  
15 spectrum (SIMS).

16 Additionally, a laser may be used to perform MALDI  
17 experiments from surface 136. In this embodiment, MALDI samples  
18 are deposited on a holder to form surface 136. A laser is used  
19 to produce ions from the MALDI samples, and the MALDI ions are  
20 extracted into the multipole 138. These ions are focused into  
21 multipole 138, cooled by collisions with the gas in multipole 138

1 and guided into analyzer 142. Mass analyzer 142 (preferably a TOF  
2 analyzer) then produces a mass spectrum from these ions - i.e. a  
3 secondary ion mass spectrum (SIMS).

4 Additionally, an IR laser may be used to irradiate ions  
5 while they are in one of multipoles 132, 140, or 138 in order to  
6 perform "in source" IRMPD in the manner described by Steven  
7 Hoffstadler.

8 Finally, other types of mass analyzers may be used instead  
9 of TOF (e.g., FTICR, quadrupole ion traps, etc.).

10 Turning next to FIG. 6, shown is an alternate embodiment of  
11 the Q-SID-Q-TOFMS according to the present invention.  
12 Specifically, depicted is a diagrammatic representation of a  
13 quadrupole surface induced dissociation quadrupole time-of-flight  
14 ("Q-SID-Q-TOF") mass spectrometer according to the invention  
15 comprising, similar to FIG. 5, ionization source 130, first  
16 multipole 132 (preferably a hexapole), second multipole  
17 (preferably a quadrupole) 140, collision surface 136 for surface  
18 induced dissociation (SID), third multipole 138 (which optionally  
19 acts as a collision cell for collision induced dissociation  
20 (CID)), and mass analyzer 142 (preferably a time of flight mass  
21 analyzer).

1       As shown in FIG. 6, the Q-SID-Q-TOF according to the  
2 invention may be used with a coaxial multiple reflection TOF mass  
3 analyzer 142, such as that described in US patent number  
4 6,107,625, which is herein incorporated by reference. Such a  
5 mass analyzer 142 comprises an "orthogonal interface" with  
6 respect to the Q-SID-Q-TOF (i.e., ion guide 138 is positioned  
7 orthogonal to the axis of the TOF analyzer 142), a drift region  
8 152, reflectron 154, detectors 144 and/or 156, accelerator 146,  
9 and optionally, multideflector 148, all oriented coaxially with  
10 one another. The mass analyzer accepts ions from the external  
11 ion source 130, via ion guides 132, 140 and 138, and accelerates  
12 them toward reflectron 154. If reflectron 154 is energized, the  
13 ions are reflected back toward detector 144. In this case the  $m/z$   
14 of the ions are determined by the time required for the ions to  
15 travel from accelerator 146 to reflectron 154, to detector 144.  
16 If reflectron 154 is deenergized, ions travel directly from  
17 accelerator 146 to detector 156. Similarly, the  $m/z$  of the ions  
18 is determined by the time required to travel from accelerator 146  
19 to detector 156. Although the TOF analyzer depicted in figure 6  
20 is a "coaxial" analyzer design, it should be recognized that any  
21 other prior art TOF analyzer design might be substituted for the

1 depicted analyzer.

2       While the present invention has been described with  
3 reference to one or more preferred embodiments, such embodiments  
4 are merely exemplary and are not intended to be limiting or  
5 represent an exhaustive enumeration of all aspects of the  
6 invention. The scope of the invention, therefore, shall be  
7 defined solely by the following claims. Further, it will be  
8 apparent to those of skill in the art that numerous changes may  
9 be made in such details without departing from the spirit and the  
10 principles of the invention. It should be appreciated that the  
11 present invention is capable of being embodied in other forms  
12 without departing from its essential characteristics.